REMARKS

Applicants would like to thank the Examiner for the personal interview granted on May 18, 2005 to Applicants' agent Donna Ward and the telephonic interview granted on April 7, 2005 to Applicants' attorney Li-Hsien Rin-Laures and Applicants' agent Donna Ward. In summary, the interview discussion focused on claim language relating to hybridization within nucleotide ranges of SEQ ID NO: 3 and to the term "non-catalytic." It was determined that amendment of the claims to eliminate nucleotide ranges, to recite a functional limitation of 30% inhibition, and to recite "non-cleaving" in place of "non-catalytic" would be looked at favorably.

I. Support for the Amendments

Support for the amendment to claims 1, 11 and 20 can be found throughout the specification. For example, support for recitation of the functional limitation "at least 30% inhibition of apoB expression when applied when applied in vitro at a concentration of 150nM to HepG2 cells" is found in Example 15 at page 88, lines 27-29 which describes that "compounds [in Table 1] were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR" and page 90, line 4, which discloses that "at least 30% inhibition of human apolipoprotein B expression in this assay [is] preferred." Additionally, Example 16, at page 91, line 24-25, teaches that selected compounds were further tested at 50, 150 and 250 nM.

Support for amendment to recite "non-cleaving" is found, for example, at page 23, lines 34, to page 24, line 4, which describes antisense compounds that do not cleave the target nucleic acid. This section states that a "region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide inhibition of gene expression."

Support for amendment to claim 2 and new claim 28, is found, for example, at page 26, lines 3-12, which describes pharmaceutically acceptable salts, including sodium salts (see also page 27, lines 29-33) of the compounds of the invention.

II. Patentability Arguments

As discussed during the personal interview of May 18, 2005, the amendments herein obviate the rejections under 35 USC §112, first paragraph.

Applicants submit that amendment of the claims to recite "non-cleaving" obviate the Examiner's rejection of claims 1-2, 4-14, and 20-23 under 35 USC §103(a) in view of Chan (WO01/12789), further in view of Branch, Monia et al., and Agrawal et al. Chan discloses use of a RNA cleaving ribozyme to modulate expression of apolipoprotein B. Branch, Monia and Agrawal assertedly disclose optimization methods for use of antisense technology.

One of ordinary skill would not look to Chan because Chan addresses ribozyme compounds that cleave RNA in contrast to the claimed compounds which do not. Ribozymes function by a completely different mechanism from the non-cleaving compounds of the present invention. The non-cleaving compounds as claimed do not directly cleave target nucleic acids, but instead recruit and/or form the basis for complexes of the target with proteinaceous RNA-cleaving enzymes. Thus, even if a ribozyme inhibited expression of a nucleic acid, one of ordinary skill in the art would not find it obvious that a non-cleaving compound targeted to the same region would successfully inhibit expression of the target nucleic acid.

Further, one of ordinary skill in the art reading Chan, in view of Branch, Monia or Agrawal would have no reasonable expectation of success at generating the non-cleaving compound having certain functional properties as claimed herein. Chan discloses only a ribozyme that binds a single site in the apolipoprotein B gene. Agrawal and Branch focus on the problems associated with successfully generating an effective antisense compound, stating that "use of PS-oligonucleotides as antisense agents might not be as simple as initially expected," (Agrawal, page 72, 2nd col.) and that "they [antisense] are far more difficult to produce than was originally anticipated," (Branch, abstract). Simply because Agrawal, Branch or Monia assertedly disclose methods for generating or optimizing an antisense compound, it does not follow that one of ordinary skill in the art has a reasonable expectation of success at generating the antisense compound disclosed herein. In contrast,

Applicants disclose antisense compounds specific for apolipoprotein B that provide effective gene inhibition.

Thus, because the cited reference Chan is not relevant to the present claims, and because the references, even if taken in combination, do not provide a reasonable expectation of success of generating the claimed non-cleaving compounds, the rejection under 35 USC. §103 should be withdrawn.

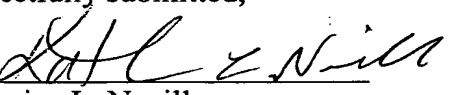
As discussed during a telephonic interview of April 7, 2005, Applicants also provide herewith a copy of Declaration Under 37 CFR §1.132 of inventor Dr. Rosanne Crooke (Exhibit 1), which was also submitted in related application no. 10/147,096. This declaration provides data confirming that compounds that target the apolipoprotein B gene at a variety of sites throughout the molecule are effective at inhibiting apolipoprotein B expression and provides measurable beneficial effects on lipid profile and glucose levels in healthy animals and animal models of disease.

III. Conclusion

In view of the amendments and remarks made herein, Applicants submit that the application is now in condition for allowance and respectfully request expedited notification of the same.

Dated: June 16, 2005

Respectfully submitted,

By 

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Agent for Applicants

Docket No.: 30566/30039
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Rosanne M. Crooke et al

Application No.: 10/147,196 Group Art Unit: 1635

Filed: May 15, 2002 Examiner: Jon B. Ashen

For: ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. ROSANNE M. CROOKE

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, Rosanne M. Crooke, declare that:

1. I am Director of the Cardiovascular Group at ISIS Pharmaceuticals, Inc., Carlsbad Research Center, 2292 Faraday Avenue, Carlsbad, California 92008. I received a Bachelors of Arts degree in Biology from Williams College in 1978 and a Doctor of Philosophy degree in Pharmacology from University of Pennsylvania in 1986. I have been employed at ISIS Pharmaceuticals, Inc. since 1989. I have been Director of the Cardiovascular Group since 2003.

2. I am a joint inventor of the subject matter described and claimed in the United States Patent Application Serial No. 10/147,196, entitled "Antisense Modulation of Apolipoprotein B Expression."

3. I am personally aware of results demonstrating that in healthy animals and in animal models of disease administration of a variety of compounds targeted to disparate regions of a mammalian ApoB genes aligning with base regions 3249-3268, 8886-8905, 8876-8895, and

10159-10178 of SEQ ID NO: 3 not only inhibited the expression of a nucleic acid molecule encoding apolipoprotein B, but also provided beneficial effects of decreasing lipid levels.

4. I previously submitted a declaration, filed May 24, 2004, in the present application describing that administration of antisense compound 301012, targeting bases 3249-3268 of the human apolipoprotein B nucleotide sequence (SEQ ID NO: 3), to healthy primates inhibited apoB expression and decreased lipid levels in these animals, including total cholesterol, HDL- and LDL-cholesterol, and triglycerides. These data confirmed the beneficial effect of antisense inhibition of apolipoprotein B *in vivo* in primates not suffering from any disease.

5. Experiments with compounds targeting alternate sites of mammalian apolipoprotein B nucleotide sequences have shown that these alternate compounds are also effective at inhibiting apolipoprotein B expression and decreasing lipid levels. The targeted sites in mammalian apoB genes align with sites in the human apolipoprotein B gene (SEQ ID NO: 3) as illustrated in Exhibit A.

6. Antisense compound 147764 disclosed in the present application targets a site in the mouse apoB gene that aligns with bases 8886-8905 of the human apolipoprotein nucleotide sequence (SEQ ID NO: 3) (see Exhibit A). Administration of antisense compound 147764 to mice fed a high-fat diet, which are susceptible to hyperlipidemia-induced atherosclerotic plaque formation, led to decreased serum apolipoprotein B levels in treated animals, and also decreased serum total cholesterol and serum LDL-cholesterol. These results show a beneficial effect of the antisense compounds in mammals susceptible or at risk of cardiovascular disease.

7. Antisense compound 147483 disclosed in the present application targets a site in the mouse apoB gene that aligns with bases 8876-8895 of the human apolipoprotein nucleotide sequence (SEQ ID NO: 3) (see Exhibit A). Antisense compounds 147483 or 147764 were administered to *ob/ob* mice, a genetic model for type II diabetes and obesity characterized by hyperlipidemia and increased triglyceride levels, both of which are associated with an increase in cardiovascular disease. ApoB and lipid levels were measured. Antisense treated *ob/ob* mice showed decreased liver apolipoprotein B mRNA, reduced serum triglycerides and reduced serum total cholesterol. These results show a beneficial effect of antisense compounds in treating

mammals susceptible or at risk for obesity, diabetes, cardiovascular disease, or other diseases associated with apolipoprotein B expression.

8. Antisense compound 233183 targets a site in the rabbit apoB gene that aligns with bases 1817-1836 of mouse apoB (SEQ ID NO: 10) and bases 10159-10178 of the human apolipoprotein B nucleotide sequence (SEQ ID NO: 3) (see Exhibit A). Administration of antisense compound 233183 to rabbits fed a normal diet decreased liver apoB mRNA levels in treated animals and reduced serum total cholesterol levels. These data confirm the beneficial effect of antisense inhibition of apolipoprotein B *in vivo* in mammals not suffering from any disease.

9. The results described above demonstrate that antisense compounds targeting a wide array of nucleotide sites (e.g. N-terminal, C-terminal, or internal nucleotide sequences) within the mammalian apolipoprotein B sequences effectively inhibit apolipoprotein expression levels in treated animals. In addition to decreasing apoB expression, the compounds also decrease lipid levels, resulting in, e.g., decreased cholesterol levels, decreased triglyceride levels and decreased LDL-cholesterol. These results confirm the statements made in the application regarding activity of the antisense compounds recited in the claims.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Date 5/13/05

Dr. Rosanne M. Crooke

Mammalian Apolipoprotein B Sequences

Human GENBANK NM_000384.1; SEQ ID NO: 3 of ISPH-0664
Mouse GENBANK M35186.1; SEQ ID NO: 10 of ISPH-0664
Rabbit sequenced at Isis; SEQ ID NO: 810 of DOC-0216US

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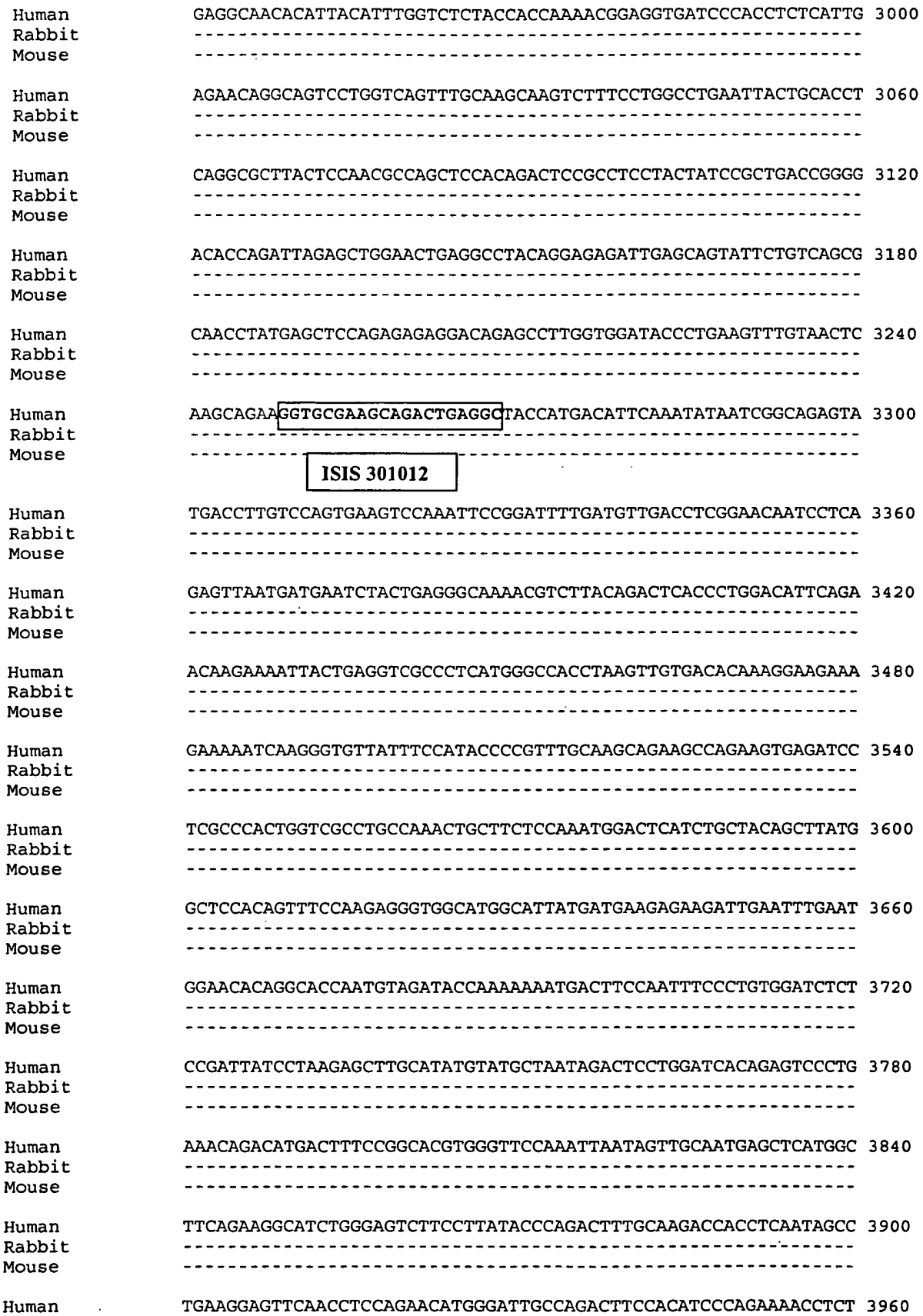
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Rabbit   ------------------------------------------------------------
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Mouse           ------------------------------------------------------------

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Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           AACACTTTGTTATAAATCTTATTGGGGATTTTGAAGTAGCTGAGAAAATCAATGCCTTCA 7140
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           GAGCCAAAGTCCATGAGTTAATCGAGAGGTATGAAGTAGACCAACAAATCCAGGTTTTAA 7200
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           AAACCAATGACAAAATCCGTGAGGTGACTCAGAGACTCAATGGTGAAATTCAGGCTCTGG 7500
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           CAGTGTATCTGGAAAGCCTACAGGACACCAAAATAACCTTAATCATCAATTGGTTACAGG 7620
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           AGGCTTTAAGTTCAGCATCTTTGGCTCACATGAAGGCCAAATTCCGAGAGACTCTAGAAG 7680
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           ATACACGAGACCGAATGTATCAAATGGACATTCAGCAGGAACTTCAACGATACCTGTCTC 7740
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           TGGTAGGCCAGGTTTATAGCACACTTGTCACCTACATTTCTGATTGGTGGACTCTTGCTG 7800
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           CTAAGAACCTTACTGACTTTGCAGAGCAATATTCTATCCAAGATTGGGCTAAACGTATGA 7860
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

Human           AAGCATTGGTAGAGCAAGGGTTCACTGTTCCTGAAATCAAGACCATCCTTGGGACCATGC 7920
Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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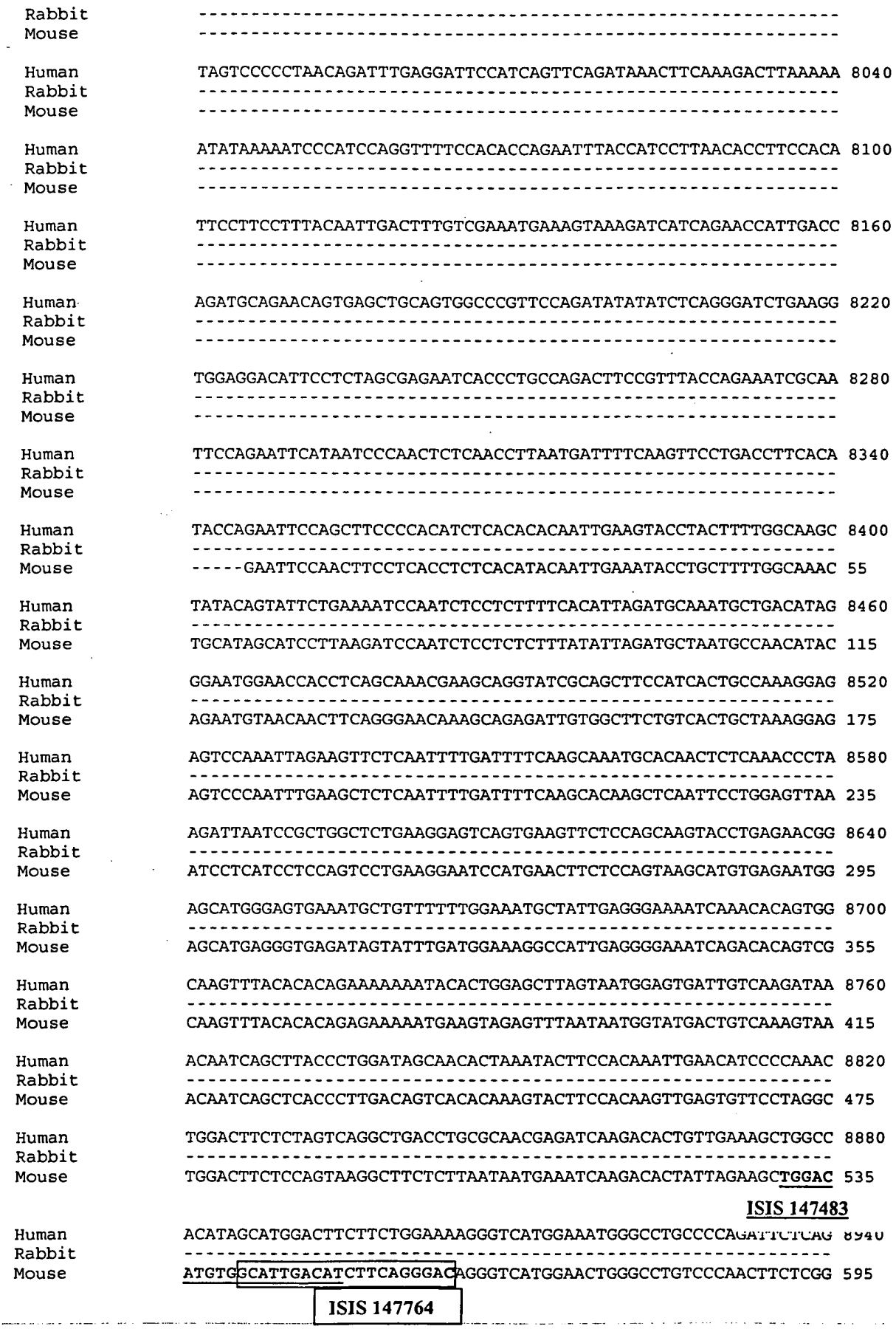
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Rabbit
Mouse
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Rabbit
Mouse
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Rabbit
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Rabbit
Mouse
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Rabbit
Mouse
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Rabbit
Mouse -----GAATTCCAACTTCCTCACCTCTCACATACAATTGAAATACCTGCTTTTGGCAAAC 55
Human TATACAGTATTCTGAAAATCCAATCTCCTCTTTTCACATTAGATGCAAATGCTGACATAG 8460
Rabbit
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Rabbit
Mouse AGAATGTAACAACTTCAGGGAACAAAGCAGAGATTGTGGCTTCTGTCACTGCTAAAGGAG 175
Human AGTCCAAATTAGAAGTTCTCAATTTTGATTTTCAAGCAAATGCACAACTCTCAAACCCTA 8580
Rabbit
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Rabbit
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Rabbit
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Rabbit
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ISIS 147483
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Human   GACTGTCCAATAAGATCAATAGCAAACACCTAAGAGTAAACCAAAACTTGGTTTATGAAT 9060
Rabbit  ------------------------------------------------------------
Mouse   GACTATCCAATAACATAAATGGCAAACACTTACGGGTCATCCAAAAACTGACTTATGAAT 715

Human   CTGGCTCCCTCAACTTTTCTAAACTTGAAATTCAATCACAAGTCGATTCCCAGCATGTGG 9120
Rabbit  ------------------------------------------------------------
Mouse   CTGGCTTCCTCAACTATTCTAAGTTTGAAGTTGAGTCAAAAGTTGAATCTCAGCACGTGG 775

Human   GCCACAGTGTTCTAACTGCTAAAGGCATGGCACTGTTTGGAGAAGGGAAGGCAGAGTTTA 9180
Rabbit  ------------------------------------------------------------
Mouse   GCTCCAGCATTCTAACAGCCAATGGTCGGGCACTGCTCAAGGACGCAAAGGCAGAAATGA 835

Human   CTGGGAGGCATGATGCTCATTTAAATGGAAAGGTTATTGGAACTTTGAAAAATTCTCTTT 9240
Rabbit  ------------------------------------------------------------
Mouse   CTGGTGAGCACAATGCCAACTTAAATGGAAAAGTTATTGGAACTTTGAAAAATTCTCTCT 895

Human   TCTTTTCAGCCCAGCCATTTGAGATCACGGCATCCACAAACAATGAAGGGAATTTGAAAG 9300
Rabbit  ------------------------------------------------------------
Mouse   TCTTTTCAGCACAACCATTTGAGATTACTGCATCCACAAATAATGAAGGAAATTTGAAAG 955

Human   TTCGTTTTCCATTAAGGTTAACAGGGAAGATAGACTTCCTGAATAACTATGCACTGTTTC 9360
Rabbit  ------------------------------------------------------------
Mouse   TGGGTTTTCCACTAAAGCTGACTGGGAAAATAGACTTCCTGAATAACTATGCATTGTTTC 1015

Human   TGAGTCCCAGTGCCCAGCAAGCAAGTTGGCAAGTAAGTGCTAGGTTCAATCAGTATAAGT 9420
Rabbit  ------------------------------------------------------------
Mouse   TGAGTCCCCGTGCCCAACAAGCAAGCTGGCAAGCGAGTACCAGATTCAATCAGTACAAAT 1075

Human   ACAACCAAAATTTCTCTGCTGGAAACAACGAGAACATTATGGAGGCCCATGTAGGAATAA 9480
Rabbit  ------------------------------------------------------------
Mouse   ACAATCAAAACTTTTCTGCTATAAACAATGAACACAACATAGAAGCCAGTATAGGAATGA 1135

Human   ATGGAGAAGCAAATCTGGATTTCTTAAACATTCCTTTAACAATTCCTGAAATGCGTCTAC 9540
Rabbit  ------------------------------------------------------------
Mouse   ATGGAGATGCCAACCTGGATTTCTTAAACATACCTTTAACAATTCCTGAAATTAACTTGC 1195

Human   CTTACACAATAATCACAACTCCTCCACTGAAAGATTTCTCTCTATGGGAAAAAACAGGCT 9600
Rabbit  ------------------------------------------------------------
Mouse   CTTACACGGAGTTCAAAACTCCCTTACTGAAGGATTTCTCCATATGGGAAGAAACAGGCT 1255

Human   TGAAGGAATTCTTGAAAACGACAAAGCAATCATTTGATTTAAGTGTAAAAGCTCAGTATA 9660
Rabbit  ------------------------------------------------------------
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Human   AGAAAAACAAACACAGGCATTCCATCACAAATCCTTTGGCTGTGCTTTGTGAGTTTATCA 9720
Rabbit  ------------------------------------------------------------
Mouse   AAAAGAACAGTGACAAGCATTCCATTGTTGTCCCTCTGGGTATGTTTTATGAATTTATTC 1375

Human   GTCAGAGCATCAAATCCTTTGACAGGCATTTTGAAAAAAACAGAAACAATGCATTAGATT 9780
Rabbit  ------------------------------CAGAACATCGGAGACAACGCATTGGATT 28
Mouse   TCAACAATGTCAATTCGTGGGACAGAAAATTTGAGAAAGTCAGAAACAATGCTTTACATT 1435
                                        * **   * ** **** ** **  ***

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Rabbit  TTCTCACTAAATCTTANAATGAAGCAAAAATTAAGTTTGATAAGTACAAAGTTGAAAAAT 88
Mouse   TTCTTACCACCTCCTATAATGAAGCAAAAATTAAGGTTGATAAGTACAAAACTGAAAATT 1495
        ** * ** *  ** ** ****** ********** ********** ****** *

Human   CTCACGACGAGCTCCCCAGGACCTTTCAAATTCCTGGATACACTGTTCCAGTTGTCAATG 9900
Rabbit  CGCTCAACAGGCTCCCCAGGACCTTTCAGNCTCCTGGATACATTATTCCAATTTTCAATN 148
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Mouse           CCCTTAATCAGCCCTCTGGGACCTTTCAAAATCATGGCTACACTATCCCAGTTGTCAACA 1555
                * *   *   ** * *  **********   ** *** **** * * *** ** ****

Human           TTGAAGTGTCTCCATTCACCATAGA-GATGTCGGCATTCGGCTATGTGTTCCCAAAAGCA 9959
Rabbit          TTGAAGTATCTCCACTCACAATAGNAGACGTNAGCATTCAGTCATGTGATCCCAAAATCA 208
Mouse           TTGAAGTATCTCCATTTGCTGTAGA-GACACTGGCTTCCAGGCATGTGATCCCCACAGCA 1614
                ******* ****** *  *  ***  **     ** * * *  ***** **** * * **

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Rabbit          ATAAGCACCCCCAATGTCACCATCCTGGATTCAAGCTTCTATGTGCCTTCATATACATTG 268
Mouse           ATAAGCACCCCAAGTGTCACAATCCCTGGTCCTAACATCATGGTGCCTTCATACAAGTTA 1674
                 * ****  ** * * ** * ****  * * *   * **   ********** *  **

Human           ATCCTGCCATCATTAGAGCTGCCAGTCCTTCATGTCCCTAGAAATCT---CAAGCTTTCT 10076
Rabbit          GCTCTGCCATCCCTAGAGCTGCCAGTCTTCCATGTCCCCAGGAATCTACTCAAGGTCTCT 328
Mouse           GTGCTGCCACCCCTGGAGTTGCCAGTTTTCCATGGTCCTGGGAATCTATTCAAGTTTTTC 1734
                   ****** *  * *** *******  * ****  **  * *****   **** * *

Human           CTTCCACATTTCAAGGAATTGTGTACCATAAGCCATATTTTTATTCCTGCCATGGGCAAT 10136
Rabbit          CTTCCAGATTTCAAGGAATTGAAAACCATTAACAATATTTTTATTCCAGCCATGGGCAAC 388
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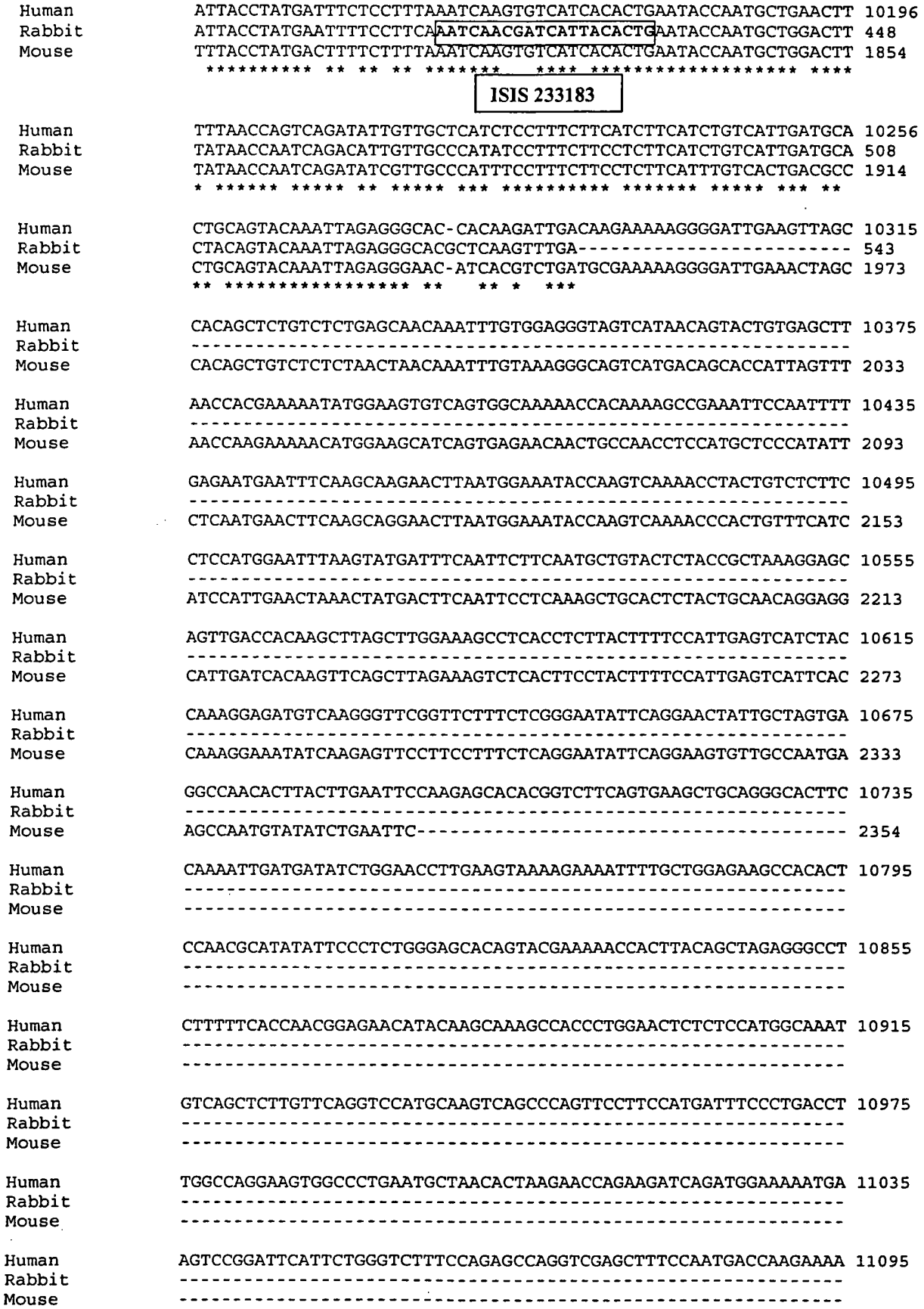
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Rabbit CTACAGTACAAATTAGAGGGCACGCTCAAGTTTGA---------- 543
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Rabbit ----------
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Rabbit ----------
Mouse ----------

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Mouse   ------------------------------------------------------------

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Mouse   ------------------------------------------------------------

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Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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Rabbit          ------------------------------------------------------------
Mouse           ------------------------------------------------------------

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Rabbit          --------------------------
Mouse           --------------------------
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